AWARD NUMBER: W81XWH-13-1-0486

TITLE: Early Recognition of Chronic Traumatic Encephalopathy through FDDNP PET Imaging

PRINCIPAL INVESTIGATOR: Charles Bernick, MD, MPH

CONTRACTING ORGANIZATION: Cleveland Clinic Foundation
9500 Euclid Ave
Cleveland, Ohio 44195

REPORT DATE: October 2016

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual Report	30Sep2015-29Sep2016

4. TITLE AND SUBTITLE

Early Recognition of Chronic Traumatic Encephalopathy Through FDDNP PET Imaging

5a. CONTRACT NUMBER
W81XWH-13-1-0486

5b. GRANT NUMBER
GRANT11277772

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S) Charles Bernick, MD, MPH

E-Mail: bernicc@ccf.org

5d. PROJECT NUMBER
PT120134

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

1. The PET biomarker, F-FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl(methyl)amino]-2-naphthyl} ethylidene) malononitrile) [FDDNP] has shown sensitivity for in vivo detection of tau in addition to β-sheet-containing brain amyloid neuroaggregates. Tau protein in a characteristic distribution is felt to be the cardinal pathologic feature of Chronic Traumatic Encephalopathy. This project will examine whether FDDNP PET imaging correlates with, and/or can predict, decline in cognitive function in those exposed to cumulative head trauma.

15. SUBJECT TERMS
Traumatic Brain Injury
Positron Emission Tomography

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	8	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

1. Introduction: Blast injuries and other head injuries sustained in battle have been associated with the development of chronic traumatic encephalopathy (CTE). Pathological series have indicated that a characteristic feature of CTE is accumulation of tau protein in the brain. Until very recently, there has been no reliable way of measuring tau deposition in the brain during life. One PET biomarker, F-FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl(methyl)amino]-2-naphthyl} ethylidene) malononitrile) [FDDNP] has shown sensitivity for in vivo detection of tau in addition to B-sheet-containing brain amyloid neuroaggregates. This project will examine whether FDDNP PET imaging correlates with, and/or can predict, decline in cognitive function in those exposed to cumulative head trauma.

2. Keywords: Traumatic Brain Injury, Chronic Traumatic Encephalopathy, PET imaging, Tau

3. Accomplishments:

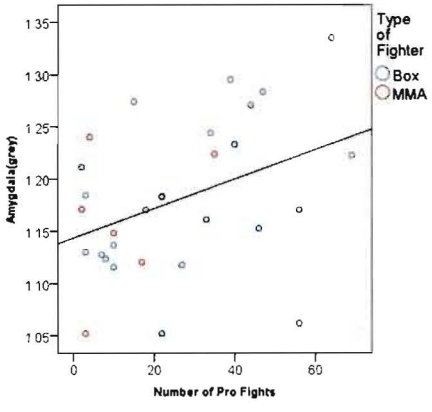
Upon receiving approval from the Human Research Protection Office, enrollment of participants began in March, 2015. We have completed 45 PET FDDNP studies, with 6 additional subjects scheduled within the next 4 weeks. Recruitment progress is reflected in the following grid:

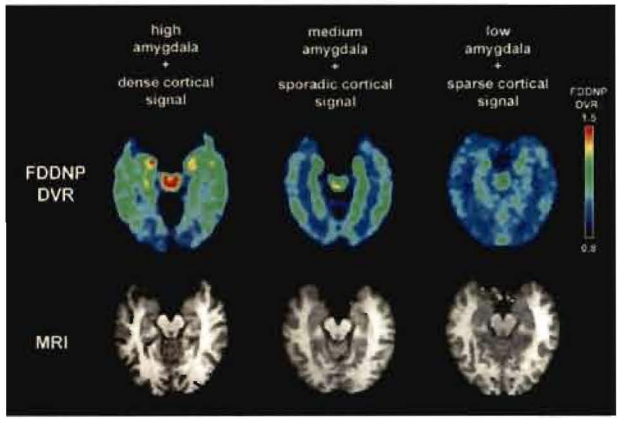
Type of Fighter	Scheduled		Completed		Req'd
	Base	2 Year	Base	2 Year	
Control	3		8		8/20
Active, Unimpaired	1	0	5	6	11 / 12
Active, Impaired	0	0	6	1	7 / 12
Retired, Unimpaired	1	1	7	1	8 / 12
Retired, Impaired	0	0	10	1	11/ 12
TOTAL:	6		45		**51 / 68**

Each subject is to be followed yearly for 3 years as part of the Professional Fighters Brain Health Study. Of the 26 participants due for follow up in 2016, 23 participants completed follow (88%retention). Of

those who are overdue for year one follow up, 2 have been unable to return due to work (we will continue attempting to schedule their follow up) and 1 is lost to follow up due to moving permanently to Australia).

Once 50% of the cohort was enrolled, we undertook several analytical approaches to the acquired data that has resulted in three abstract presentations. Traditionally, PET FDDNP images were analyzed using manually drawn region of interests (ROI). Because this is not likely to be a clinically practical method of interpreting the images, the FDDNP data were processed using the automated MIAKAT (Imanova) kinetic analysis software. Parametric images of distribution volume ratio (DVR) were generated with the cerebellum as the reference region. Regional DVR measurements were obtained using the built-in brain template with gray mask applied. The results indicate a relationship between increased exposure to head trauma (measured by number of fights) and increased FDDNP uptake in the amygdala and other temporal lobe structures





In addition, there was an association between increased uptake in the parahippocampal cortex and worse performance on several cognitive measures:

Table 3: Uptake and cognitive tests	Verbal Memory	Processing Speed	Psychomotor Speed	Reaction Time
amygdala,	ns	ns	ns	Ns
hippocampus	ns	ns	ns	Ns
parahippocampal gyrus	ns	-.437*	-.313	.374
brainstem	ns	ns	ns	Ns
temporal	ns	ns	ns	Ns

We have also conducted analyses of the FDDNP images using manual ROI techniques. While many

areas of uptake were strongly associated with age, there does appear to be a relationship between FDDNP uptake and both exposure (total number of fights) and reaction time in the lateral temporal lobe.

This project has provided a training opportunity for our post –doctorate student, Bern Lee, who has worked on assessing the relationship between FDDNP imaging results and neuropsychological measures.

Preliminary results noted above have been accepted for presentation at three national conferences: Lancet Neurology Conference on Preclinical Neurodegenerative Disease (London, 10/16), Human Amyloid Imaging (Miami, 1/17), International Neuropsychological Society (New Orleans, 2/17).

Over the next reporting period, emphasis will be placed on completing enrollment (hopefully by 7/17) and continuing follow up of the subjects. We will also be exploring different methods of image analysis taking into account the problems that we have identified so far (see #5), as well as examining further potential relationships between imaging modalities (PET FDDNP and MRI).

4. **Impact:**

At the current stage, the impact from this project is limited. The preliminary data we have presented has extended what we know about PET FDDNP imaging beyond the small series that was done with retired football players.

5 **Changes/Problems:**

The major problem we have encountered is with rate of recruitment, particularly for control subjects. Several factors that slowed enrollment were: 1) the unavailability of the FDDNP tracer over the month of December, 2) Replacement of our MRI scanner during October and November (because we coregister the PET scan with the MRI image, we had to postpone enrollment during that time). Both issues have now been resolved.

We have broadened our recruitment efforts by tagging on to other studies at our center that will be recruiting control subjects, as well as continuing to reach out to other organizations in the community. Given that age seems to have an important relationship to FDDNP uptake, we have placed particular attention to enroll control subjects that are adequately matched for age with our subjects.

In order to complete the 3 year follow up of subjects, we will need to extend the completion date accordingly.

Another challenge that has arisen as we have completed preliminary analyses of the imaging is determining the optimal way to interpret the scans. Because the distribution of tau in Chronic Traumatic Encephalopathy tends to be more widespread and heterogeneous, examining small ROIs may fail to detect specific patterns of FDDNP uptake. Thus, we plan to explore assessment of uptake in clusters of

regions that may result in a more reliable means to detect abnormal tau deposition.

6. **Products:**

The following conference presentations have been presented at national conferences:

Sarah J. Banks, Vladimir Kepe, Frank DiFilippo, Jorge Barrio, and Charles Bernick. **Regional FDDNP Uptake in Relation to Professional Fight Exposure (Lancet Neurology Preclinical Neurodegenerative Disorders, London, 10/16)**

Sarah J. Banks, Vladimir Kepe, Frank P. DiFilippo, Bern Lee Jorge Barrio, and Charles Bernick **Regional FDDNP Uptake and Exposure to Professional Fighting (Human Amyloid Imaging, Miami, 1/17)**

Bern G. Lee, Charles Bernick, Vladimir Kepe, Frank P. DiFilippo, & Sarah J. Banks. **[F-18]FDDNP Uptake, Neurocognition, and Number of Fights in Professional Boxers and MMA fighters (International Neuropsychology Society, New Orleans, 2/17)**

No other products resulted from this study over the last year.

7. **Participants and other Collaborating Organizations**

The individuals who have worked on this project include:

Charles Bernick – no change

Sarah Banks – no change

Jorge Barrio - no change

Vladimir Keppe -

Project role - Image analyst

Contribution to project - Processing of PET FDDNP Images

Funding Support – Cleveland Clinic

Frank DiFillipo –

Project role – image analyst

Contribution to project – Processing of PET FDDNP Images

Funding Support – Cleveland Clinic

8. Quad Chart

Early Recognition of CTE through PET FDDNP Imaging
PT120134

PI: Charles Bernick Org: Cleveland Clinic Award Amount: $746,068

Study/Product Aim(s)

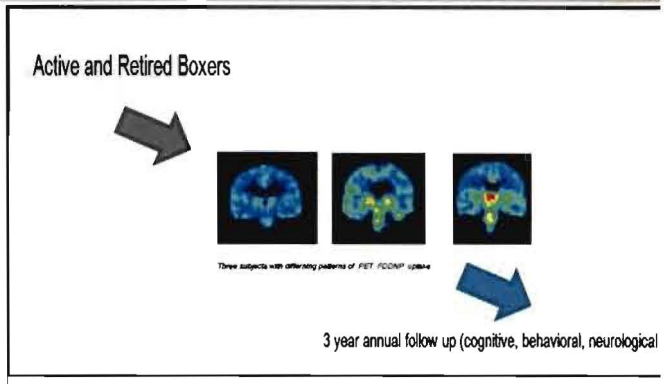
•**Study**: Exam the performance of PET FDDNP in a group of active and retired professional boxers and non trauma exposed controls.

•**Outcomes**: To determine if PET FDDNP imaging may be a potential biomarker of and diagnostic tool for CTE

Approach

- Cohort derived from the Professional Fighters Brain Health Study
- Active and retired boxers , both cognitively normal and cognitively impaired
- Subjects undergo baseline PET FDDNP imaging and followed annually with cognitive, behavioral, and neurological testing

xt.



Timeline and Cost

Activities	15	16	17	18	19	20
Baseline PET FDDNP						
Annual MRI, cognitive, behavioral assessments						
Analysis						
Estimated Budget ($K)	**$304**	**$302**	**$46**	**$46**	**$ 48**	

Goals/Milestones

CY13 Goal – Develop SOP and train coordinator
IRB Submission
Finalize logistics of transfer of FDDNP from production to site

CY14 Goals - IRB approval obtained
HRPO approval obtained
Identified eligible subjects

CY15 Goal – Enrollment of subjects, 1st subject enrolled 3/15

CY16 Goal – Continue enrollment and begin annual follow up visits, analyses

CY 17 Goal - Complete enrollment and continue annual follow up visits, analyses

Comments/Challenges/Issues/Concerns

- Delay in completion of service agreement/IRB approval/HRPO approval delayed initial enrollment; PET FDDNP imaging began 3/15. MRI scanner replacement slowed 2016 enrollment. Projected enrollment completion 7/16..